



The body has different types of fat, or adipose, tissue. This figure illustrates various biological molecules that can increase fat burning and heat production by activating brown adipose tissue or by inducing the formation of fat-burning cells within white adipose tissue—normally a storage depot for fat—in a process known as “browning.” Cold temperatures can also increase fat burning by adipose tissue. As described in this chapter, these research discoveries have implications for strategies to improve metabolic health.

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# Obesity

**O**besity has risen to epidemic levels in the United States. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission. More than one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.<sup>1</sup> Nearly 17 percent of children and teens ages 2 through 19 are also obese, and thus at increased risk for developing serious diseases both during their youth and later in adulthood.<sup>1,2</sup> Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically disadvantaged.

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also modify biologic factors in ways that promote obesity. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions.

The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental interventions in families, schools, health care, and other settings using a variety of approaches and technologies; medical and surgical interventions; and combinations of these strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches. To help bring research results to those affected by obesity and their families, health professionals, and the general public, the Institute sponsors health information programs.<sup>3</sup>

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK

Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. These represent examples of the NIDDK's broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

## OBESITY RISK FACTORS

**In the Loop—A New Obesity-associated Gene, *IRX3*, and a Strategy To Track Down Other Genes That Affect Health:** Researchers discovered that the *IRX3* gene is associated with obesity by finding that it interacts with a segment of DNA in another gene, *FTO*, that contains genetic variants previously implicated in obesity. The *IRX3* and *FTO* genes reside some distance from each other along a stretch of DNA, and the

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<sup>1</sup> Ogden CL, et al. *JAMA* 311: 806-814, 2014.

<sup>2</sup> For children and adolescents, obesity refers to a BMI at or greater than the 95<sup>th</sup> percentile on growth charts (which are based on previous national surveys).

<sup>3</sup> NIDDK Weight-control Information Network, <http://win.niddk.nih.gov/index.htm>

intervening DNA loops around to connect *IRX3* to the variant-containing region of *FTO*.

The scientists began with a conundrum from prior research: variants in the *FTO* gene's DNA sequence are associated with risk for obesity, but these variants are not in the part of *FTO* that codes for its protein product. Rather, they are in other regions of the gene (called introns). Moreover, although “non-coding” regions in or near genes can serve regulatory functions, these variants do not appear to regulate *FTO* gene activity. With a hunch that these perplexing variants might control the activity of another gene, the scientists widened their search for clues across genomic terrain both near and far from *FTO*. The researchers thought that they could trap the variants interacting with another gene because DNA strands bend and loop, bringing distant segments of the genome together so that regulatory factors can dock at one point and grasp onto a gene farther away. Using a technique devised by other scientists to capture these loops, they found that the variant-containing region of *FTO* connects with the *IRX3* gene in mice. Further study showed similar interactions in human cells. They also found that this part of *FTO* helps increase levels of *IRX3* gene activity, and that obesity-associated variants in this region correlate with differences in *IRX3* activity in the human brain. To determine more directly whether *IRX3* plays a role in weight and metabolism, the researchers investigated whether removing it from mice would have any effect. Compared to normal mice, the *IRX3*-deficient mice weighed less, had less body fat overall, and, interestingly, had more active “brown fat”—a type of fat tissue that burns rather than stores calories. Even within the calorie-storing fat tissue of these mice, some cells had taken on brown fat traits. Mice without *IRX3* were also protected from adverse metabolic consequences of a high-fat diet, including elevated blood glucose (sugar) and excess liver fat. The effects on diet were found in an experiment with male mice; future study could determine whether or not *IRX3* deficiency confers similar protection from an unhealthy diet in females.

This research yields novel insights into obesity and metabolism, which may spark new ideas for therapeutic

development. Like the variants in the non-coding part of *FTO* that led scientists to the *IRX3* gene, there are numerous other genome variants that are associated with health conditions but that do not disrupt protein-encoding parts of genes. This study thus also demonstrates the value of research to explore whether such variants might regulate gene activity—even of a distant gene.

*Smemo S, Tena JJ, Kim KH, ...Nóbrega MA.*

*Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature 507: 371-375, 2014.*

### **Nourishing Body and Mind—Effects of Maternal Diet on Brain Wiring and Metabolism in Offspring:**

Seeking to understand how a mother's health and diet during pregnancy can affect the children, researchers discovered, in mice, that a maternal high-fat diet disrupts the wiring of brain circuitry and fuels the development of excess body fat and other metabolic conditions in the offspring.

The researchers first pinpointed a critical time for the dietary effects by feeding mice either standard chow or a high-fat diet during pregnancy and lactation. A high-fat diet was most detrimental to the mouse pups when given to their mothers exclusively during lactation, a stage similar to the third trimester of human pregnancy. Within a few weeks, mice born to mothers on this unhealthy diet developed excess body fat along with signs of prediabetes and type 2 diabetes (insulin resistance and glucose intolerance). Based on clues from prior studies, the scientists then traced the connections among cells in a region of the brain called the hypothalamus, which plays a key role in regulating metabolism. In the offspring of mothers fed the high-fat diet during this stage of development, brain cells did not branch out normally to build a dense network of connections. Instead, these mice had many fewer fibers linking different areas of the hypothalamus. From additional experiments, the scientists found that the adverse dietary effects result, in part, from elevated signaling by the hormone insulin in the brains of the young mice. Other biologic pathways, yet to be defined, also play a role.

Because diabetes and obesity in women during pregnancy are known to increase risk for diabetes and obesity in their children, this study of a high-fat diet in mice may have implications for human health. Further research may lead to improved strategies for healthy eating and other interventions during pregnancy, to benefit women and their children.

*Vogt MC, Paeger L, Hess S, ...Brüning JC. Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high-fat feeding. Cell 156: 495-509, 2014.*

## **MICROBIOME, DEVELOPMENT, AND OBESITY**

### **Antibiotic Exposure in Early Life Changes Gut Microbes, Long-term Metabolism, and Immune**

**Function:** Researchers have used a mouse model to show that even short-term exposure to antibiotics early in life can transiently alter the gut microbial community, or “microbiome,” resulting in lasting effects on metabolism, weight gain, and immune function. The first few years of life are a critical time for healthy growth and development, including establishment of a healthy gut microbial community. Children raised in countries such as the United States routinely have their microbial communities altered by receiving antibiotics, which have been associated with a greater risk of obesity later in life. Also, based on decades of agricultural practice, antibiotics are known to increase weight gain in livestock, particularly if used from a young age. However, antibiotics do not cause weight gain in animals lacking gut microbes, suggesting the microbes play a key role in altered metabolism following antibiotic treatment.

One research group investigated in a mouse model the alterations occurring with antibiotic treatment in early life. Using both male and female mice, the researchers studied timing of antibiotic exposure and gut microbial changes, altered metabolic and immune indicators, and interactions with diet and resulting obesity risk. They first looked at mouse pups whose mothers had been given penicillin in drinking water right before birth and prior to weaning. Both male and female pups whose mothers received the antibiotic were bigger and had

more fat mass than the controls as adults, including in the liver, where their fat cell production genes were more active. Mice treated directly with antibiotics from a young age also showed altered shifts in the maturing gut microbial composition as they grew, compared to untreated mice. To look at how gut microbes interact with diet in mice given antibiotics, the researchers fed some of the antibiotic-treated mice a high-fat diet after weaning. In both the male and female mice, the combination of early antibiotics and high-fat diet led to a large increase in weight gain by 30 weeks (adulthood in mice), particularly in the female mice, who doubled their fat mass. When the researchers looked at metabolic changes throughout the body in these mice, they found fatty livers, especially in the male mice, as well as changes in the activity of genes associated with carbohydrate and fat metabolism. Similar effects on weight gain were found in mice given just a limited course of antibiotic for 4 to 8 weeks during early life and fed the high-fat diet. These mice also had reduced activity of cells and genes involved in intestinal immunity. Surprisingly, following the short-term antibiotic exposure, the mice’s gut microbe populations slowly returned to a normal mix of bacterial species, even though the metabolic effects persisted. Finally, the researchers were able to transfer this altered metabolism between individuals by transplanting the antibiotic-treated mice’s intestinal contents into the sterile guts of germ-free mice. This showed that it was changes in the gut microbes themselves, not direct effects of the antibiotic, causing the altered metabolism.

These studies show that changes early in life in the structure of the gut microbial community, due to factors such as antibiotics, could have life-long consequences by “programming” an organism’s future metabolism and immune function. If these results in mice hold true for humans, they would provide compelling reasons for devising ways to restore normal gut microbial composition in children exposed to antibiotics, both to reduce risk of metabolic disorders and establish healthy immunity.

*Cox LM, Yamanishi S, Sohn J, ...Blaser MJ. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 158: 705-721, 2014.*

## **BARIATRIC SURGERY—SAFETY AND EFFICACY**

### **Bariatric Surgery Yields Significant but Variable Weight Loss and Health Improvements After**

**Three Years:** A new study has found that adults with severe obesity had substantial weight loss 3 years after bariatric surgery, with significant improvements in diabetes, high blood pressure, and cholesterol outcomes. The researchers also found that weight loss and other outcomes varied among the study participants. People with severe obesity often do not gain sufficient health benefits from lifestyle interventions alone, and thus may turn to bariatric surgery, in addition to lifestyle changes, to help them lose weight and reduce their risk for obesity-associated health conditions. However, the generalizability of previous reports assessing the medium- and long-term risks and benefits of bariatric surgery has been limited. The multi-center Longitudinal Assessment of Bariatric Surgery (LABS) Consortium was launched to assess the safety and efficacy of bariatric surgery procedures with standardized, detailed data collection from a geographically diverse cohort of study participants across the country to provide evidence that can be broadly applicable to clinical practice.

In a new report from the LABS Consortium, more than 2,000 adults underwent either Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB)—two different commonly performed bariatric surgery procedures. About 80 percent of the initial group of study participants were women. Significant weight loss was observed 3 years after surgery, with the majority of participants losing the most weight during the first year. There were, however, differences in the extent of weight loss between the two procedures. There was also substantial variation among individuals who had the same procedure; for each procedure, the weight loss trajectories of the study participants were not uniform, but fell into five distinct groups. Some lost more weight during the study and experienced only a small amount of weight regain, while others lost less and gained more of their weight back more quickly. Overall, the median weight loss for individuals who underwent RYGB was 31.5 percent of the body weight they had

before surgery, compared with 15.9 percent weight loss for those who had LAGB surgery. The scientists also observed significant improvements in obesity-associated health conditions, but again with differences between the two procedures. Many participants had at least partial remission of type 2 diabetes (67.5 percent for those who had RYGB and 28.6 percent for those who had LAGB, respectively), improvements in high blood pressure (38.2 percent and 17.4 percent, respectively), and a reduction in excess fats in the bloodstream (61.9 percent and 27.1 percent, respectively). Thus, RYGB, and to a lesser degree LAGB, leads to significant weight loss and reduction in obesity-related health conditions, but the extent of these improvements is variable. Factors such as the large number of individuals enrolled in the study, standardized data collection, and diversity of geographic locations where the surgeries took place add to the generalizability of the findings from this report. To determine the durability of these results, LABS researchers are conducting longer-term follow-up analyses of participants' health and weight.

*Courcoulas AP, Christian NJ, Belle SH, ... Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA 310: 2416-2425, 2013.*

### **Bariatric Surgery in Teens Leads to Relatively Few Short-term Complications:**

In a new study in adolescents with severe obesity and weight-related health problems who underwent bariatric surgery, researchers found few incidents of major complications in the first 30 days after the surgery. Children and teens who are obese—and particularly those with severe obesity—are at increased risk for developing serious diseases both during their youth and later in adulthood. In youth, obesity is often accompanied by other adverse health conditions, such as sleep apnea, joint pain, hypertension, and nonalcoholic fatty liver disease. For adolescents who are severely obese, lifestyle changes are important, but when lifestyle interventions alone do not reduce obesity and ameliorate its associated health conditions, additional therapies may be considered, such as surgery. However, despite the use of this surgery in clinical practice in adolescents,



there has been limited data on its outcomes. Thus, the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study was launched in 2007 to assess the short- and long-term risks and benefits of bariatric surgery among teens with severe obesity. This is an observational study that enrolled teens who were already planning to have bariatric surgery.

Researchers from five U.S. Teen-LABS centers have now analyzed and reported short-term outcomes of three bariatric surgery techniques: Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding. A cohort of 242 study participants, aged 19 and under, was evaluated for major, or life-threatening, complications (*e.g.*, bowel obstruction/bleeding, gastrointestinal leaking, deep vein thrombosis, splenectomy), as well as for minor (non-life-threatening) complications (*e.g.*, pneumonia, urinary tract infections or other complications, bowel injury, hypertension). At 30 days after surgery, there were no deaths; 8 percent of the participants experienced major complications; and 15 percent experienced minor complications. Thus, over the short-term, bariatric surgery led to relatively few complications. While the study is limited by a lack of ethnic diversity, the standardized data collection procedures, multi-site enrollment, and comprehensive study design provide valuable information that could help inform health care providers. Importantly, Teen-LABS investigators will continue to study the participants to determine longer-term safety, health, and weight outcomes of bariatric surgery in teens.

*Inge TH, Zeller MH, Jenkins TM, ...Buncher R; Teen-LABS Consortium. Perioperative outcomes of adolescents undergoing bariatric surgery: the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. JAMA Pediatr 168: 47-53, 2014.*

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*For more information on bariatric surgery, please see the Story of Discovery later in this chapter and also “Comparing Surgical and Non-surgical Treatments for Type 2 Diabetes in Adults Who Have Mild to Moderate Levels of Obesity” on page 20.*

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## FUNCTION OF BROWN FAT

**Cool Temperature Alters Human Brown Fat and Improves Insulin Sensitivity:** New research shows that, in men, prolonged exposure to a cool environment increases brown fat volume and energy expenditure. Mammals harbor different types of fat tissue: calorie-storing white adipose tissue (WAT) is the most abundant; brown adipose tissue (BAT), which burns calories to generate heat; and beige fat tissue, which exhibits some characteristics of classic BAT cells but also has distinct properties, and can appear within WAT depots in response to various triggers. Because of its calorie-burning properties, scientists have considered BAT a promising target tissue for the development of treatment strategies for obesity. However, how BAT is regulated in humans, whether its volume can change dynamically, and its effects on metabolism remain poorly understood.

A team of scientists has now explored the effects of ambient temperature on brown fat and metabolism in five healthy men with an average age of 21 years old. The study participants resided for 4 months in a clinical research unit in the NIH Clinical Center in Bethesda, Maryland. The men engaged in regular activities during the day and then returned to their private room each evening. The temperature of the room was set to 75 degrees Fahrenheit during the first month, 66 degrees the second month, 75 degrees again for the third month, and 81 degrees the remaining month. The participants were exposed to the temperature for at least 10 hours each night. They wore standard hospital clothing and had only bed sheets. All meals were provided, with calorie and nutrient content carefully controlled and all consumption monitored. At the end of each month, the men underwent extensive evaluations, including energy expenditure testing, muscle and fat biopsies, and imaging of an area of the neck and upper back region to measure BAT volume and activity. After a month of exposure to mild cold (*i.e.*, 66 degrees), the participants had a 42 percent increase in brown fat volume and a 10 percent increase in fat metabolic activity. These alterations returned to near baseline during the following month of neutral temperature,

and then were completely reversed during the final month of warm exposure. All the changes occurred independently of seasonal changes. The increase in brown fat following a month of cold exposure was accompanied by improved insulin sensitivity after a meal during which volunteers were exposed to mild cold. Prolonged exposure to mild cold also resulted in significant changes in metabolic hormones. There were no changes in body composition or calorie intake. While this study included a relatively small number of people, and only men, these proof-of-concept findings suggest that humans

may acclimate to cool temperature by increasing brown fat, which in turn may lead to improvements in metabolism—changes that can be dampened or reversed following exposure to warmer temperatures.

*Lee P, Smith S, Linderman J, ...Celi FS. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. Diabetes 63: 3686-3698, 2014.*

*(Information adapted from original article by Dr. Carol Torgan, published on July 8, 2014 in NIH Research Matters.)*

# *To Beige or Not To Beige: Novel Molecular Insights into the Induction of a Calorie-burning Fat Tissue*

*Several recent studies supported by the NIDDK revealed the roles of various biological molecules in turning one type of body fat tissue into another type of fat in mice and people. This research has implications for strategies to improve metabolic health.*

Mammals harbor different kinds of adipose (fat) tissue in various regions of the body. Calorie-storing white adipose tissue (WAT) is the most abundant type of fat tissue. In contrast to WAT, brown adipose tissue (BAT) burns calories to generate heat. Research has shown that another type of brown fat cells—called beige fat cells—exhibits some characteristics of classic BAT cells, such as an active program of genes involved in generating heat, but also have distinct properties. These beige fat cells appear within WAT depots (a process referred to as the “browning” of WAT) in response to cold, other nervous system triggers, and muscle activity. The metabolic potential of beige fat has led many researchers to believe that it could serve as a target for treatment strategies in humans, but the molecular control of beige fat induction remains poorly understood. A series of new studies has shed light on the molecules and pathways that regulate beige fat.

In one report, researchers genetically modified mice to lack the protein PRDM16 in adipose tissues. The resulting mice lost the ability to induce beige fat cells specifically in subcutaneous WAT, which is found just under the skin. These mice developed obesity, insulin resistance, and elevated fat accumulation in the liver. In addition, the subcutaneous fat tissue shifted form to resemble visceral fat tissue, which is the type of fat that surrounds internal organs and is associated with risk for type 2 diabetes. These findings demonstrate that, in mice, beige fat contributes to the overall metabolic health of the animal and PRDM16 in WAT is required for the induction of beige fat cells.

Previous research has shown that exercise can induce beige fat production, but what molecular signals trigger

this “browning” of WAT? In a recent study, scientists identified a metabolite, called  $\beta$ -aminoisobutyric acid, or “BAIBA,” that is produced by muscle tissue following exercise and can induce the “browning” of WAT. When mice were either put on an exercise program or genetically modified to resemble mice that have undergone exercise, BAIBA levels were elevated in muscle tissue and in circulating blood compared to normal mice. Mice fed BAIBA exhibited decreased body fat, increased energy expenditure (calorie burning), improved glucose (sugar) tolerance, and a slight, but significant, reduction in weight. To see if humans similarly produce BAIBA, the scientists examined participants in the HERITAGE Family Study and found that, after a 20-week exercise program, blood BAIBA levels increased by 17 percent—a response similar to that observed in rodents. The researchers also examined levels of the metabolite in blood samples of participants in the landmark Framingham Heart Study, which has followed participants for long periods of time to identify cardiometabolic risk factors. They found that higher levels of circulating BAIBA were associated with reduced cardiometabolic risk, including reduced insulin resistance and lower levels of fasting glucose, insulin, triglycerides, and total cholesterol. These findings reveal a novel link between an exercise-induced, secreted metabolite from muscle tissue and beige fat production and improved metabolic health.

Another molecular trigger of beige fat induction was also recently identified, that links exercise to the activation of immune cells within WAT. Scientists searched in mice for signals that were being sent from muscle cells engineered to contain high levels of PGC-1 $\alpha$ —a protein in muscle that induces a signal capable of triggering the “browning” of WAT. The researchers identified the little-known protein hormone Meteorin-like, or “Metrl,” as an important mediator of this communication. Interestingly, the scientists found that in mice, as well as in male



human study participants, exercise leads to the production of Metrnl in the muscle and its release into the bloodstream. In mice, mild exposure to cold temperatures induces production of Metrnl in fat tissue. To better understand Metrnl's function, the researchers generated experimentally modified male mice that, in the absence of exercise, could produce the hormone—not in their muscles, but in their livers—and secrete it into the bloodstream. In these mice, they observed characteristic “browning” of WAT, similar to that seen in mice with high levels of PGC-1 $\alpha$ 4. The mice with liver-produced Metrnl also were protected from some of the negative effects of a high-fat diet: they exhibited improved glucose tolerance and increased energy expenditure, a physiological feature that is associated with thermogenesis. However, Metrnl did not appear to act directly on white fat cells; rather, it appeared to trigger the stepwise activation of a number of types of immune cells that normally reside within WAT, some of which have been previously implicated in the “browning” of WAT. One type of immune cell, called an eosinophil, produces proteins, called IL-4 and IL-13 (referred to collectively as “IL-4/IL-13”), in response to Metrnl. The researchers found that exposure to cold temperatures increases the levels of *IL-4/IL-13* gene activity, and blocking the action of IL-4/IL-13 protein prevents thermogenic genes from being induced in WAT in response to Metrnl. IL-4/IL-13 may increase thermogenesis by inducing another type of immune cell, called an “alternatively activated” macrophage. These results provide a link between exercise and the “browning” of WAT through activation of immune cells.

These results were supported by a separate study, in which scientists exposed male mice that were genetically modified to lack the *IL-4/IL-13* genes to mild cold stimulation and examined their ability to induce “browning” of WAT—that is, the induction of beige fat. In contrast to normal mice, the mutant mice failed to stimulate beige fat cell production within subcutaneous WAT in response to cold exposure, and the scientists did not detect the accompanying characteristic robust energy expenditure. The researchers observed similar results with mice in which eosinophils were genetically ablated from WAT. Other experiments demonstrated

that IL-4/IL-13 may promote alternative activation of macrophages, which in turn induce the browning of WAT. When the scientists administered IL-4 to normal male mice that were not exposed to cold temperature, they observed the induction of thermogenic genes in WAT and increased energy expenditure; these mice, when fed a high-fat diet, were also protected from the metabolic dysfunction seen in untreated mice. Taken together, these results strongly support a role for eosinophils, IL-4, and alternatively activated macrophages in cold-induced “browning” of WAT—cells and signaling molecules also involved in exercise-induced browning of WAT, as reported by the other researchers.

Understanding the molecules and processes contributing to beige fat development and function could also lead to previously unforeseen health benefits for other diseases. Cachexia is a dramatic loss of skeletal muscle mass and adipose tissue often accompanied by substantial weight loss and frailty, and is commonly associated with sepsis and cancer. Previous research implicated BAT induction and activation in the increased resting energy expenditure associated with cachexia in animals. Scientists have now found that in a mouse model for lung cancer, tumors send a protein signal, called PTHrP, which induces and activates beige and brown fat. In male mice with lung cancer, blocking the activity of PTHrP led to reduced “browning” of WAT, decreased heat production, and improvements to the cachectic condition. Thus, although increased beige fat mass and activity may provide benefit in the setting of obesity and diabetes, in the case of cachexia the induction of brown or beige fat by PTHrP is associated with adverse effects. The researchers also examined 47 human lung or colon cancer patients with cachexia, and found that elevated levels of PTHrP in the blood were associated with less muscle mass and increased resting energy expenditure. These results suggest that PTHrP may be playing a similar role in people and could be a target for cancer-related cachexia.

These studies provide important new insights into the mechanisms regulating beige fat induction, as

well as its associated metabolic effects, both in normal physiology and in disease progression. Most of these experiments were performed in animal models, but some initial human studies support a role for beige and brown fat in improved metabolic health. (For one example, please see the advance entitled “Cool Temperature Alters Human Brown Fat and Improves Insulin Sensitivity,” also in the Obesity chapter.) While further investigation in humans is needed, these promising findings could aid in the development of therapeutic strategies for obesity and associated metabolic diseases that promote the “browning” of WAT.

*Cohen P, Levy JD, Zhang Y,...Spiegelman BM. Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. Cell 156: 304-316, 2014.*

*Kir S, White JP, Kleiner S,...Spiegelman BM. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature 513: 100-104, 2014.*

*Qiu Y, Nguyen KD, Odegaard JI,...Chawla A. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell 157: 1292-1308, 2014.*

*Rao RR, Long JZ, White JP,...Spiegelman BM. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell 157: 1279-1291, 2014.*

*Roberts LD, Boström P, O'Sullivan JF,...Gerszten RE.  $\beta$ -aminoisobutyric acid induces browning of white fat and hepatic  $\beta$ -oxidation and is inversely correlated with cardiometabolic risk factors. Cell Metab 19: 96-108, 2014.*

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*Another study, not supported by the NIDDK, showed substantial “browning” of intestinal fat tissue and fat surrounding the liver, kidney, and pancreas in patients with cachexia, secondary to a variety of cancers—findings that complement those from the study described in the feature above (Cell Metab 20: 433-447, 2014).*

# STORY OF DISCOVERY

## *Understanding the Health Benefits and Risks of Bariatric Surgery*

Severe obesity is a chronic condition that, for many people, is difficult to treat with diet or exercise alone, and increases risks for type 2 diabetes, cardiovascular disease, fatty liver disease, and many other devastating health conditions. Bariatric surgical procedures, which restrict stomach size and/or alter the intestinal tract, have been increasingly performed to treat severe obesity when other interventions have not worked. Additionally, bariatric surgery is used in clinical practice for people who have milder levels of obesity along with type 2 diabetes or other serious obesity-related disease. These surgical procedures can have dramatic benefits—such as significant and sustained weight loss, improved control of blood glucose (sugar) levels, or even reversal of type 2 diabetes—especially when accompanied by exercise and a healthy diet. They also carry substantial risks, and researchers have been evaluating the benefits and risks of different procedures.

Despite the increasing popularity of bariatric surgery, crucial questions still remain, such as how best to select candidates for surgery, based on improved definition of specific benefits versus short- and longer-term complications and survival rates, and the effects of different procedures on specific co-morbidities in people with lesser degrees of obesity. While the surgical modifications of the stomach and intestines reduce food intake and the amount of nutrients—including calories—absorbed, emerging evidence is revealing potential additional mechanisms for the effects on weight and metabolism. Researchers would thus like to determine precisely how certain types of bariatric surgical procedures work to help patients lose a considerable amount of weight,

maintain weight loss, and improve obesity-related diseases. Finally, there is as yet unexplained heterogeneity in the outcomes of bariatric surgery, ranging from dramatic weight loss and improvement in comorbidities to subsets of patients who fail to lose weight, or who regain weight, and do not have a satisfactory outcome.

Scientists supported by the NIDDK and other organizations have been studying the risks and benefits of bariatric surgery, to help individuals with obesity and their doctors make more informed decisions. Additionally, research on the underlying mechanisms for the effects of bariatric surgical procedures could lead to the development of novel, non-surgical treatments that confer the benefits without the risks of surgery.

### **Bariatric Surgical Procedures**

The first surgery of this type used for severe obesity dates back 50 years and grew out of the results of operations for certain cancers or severe ulcers. Doctors became aware that their patients lost weight following surgeries that removed large portions of the stomach or small intestine. Some physicians began to use such operations to treat patients with severe obesity. Over time, these operations have been modified to improve patient safety and to incorporate technological advances in surgical procedure. There are several general problems involved in assessing the outcomes of bariatric surgery. One is that new surgical approaches and technologies evolve continuously, and are continuing to change at the present time. Secondly, the patient populations who receive bariatric surgery

# STORY OF DISCOVERY

also continue to evolve and may be quite different in individual studies. Together, these issues often make direct comparisons of research studies difficult.

There are several different surgical procedures performed that work through restricting food intake, changing the way in which food is absorbed or metabolized, or both. Physicians performing restrictive operations such as the laparoscopic adjustable gastric banding (LAGB) reduce the opening to the stomach or stomach size. Other procedures such as the biliopancreatic diversion, with or without duodenal switch, restrict the amount of calories and nutrients the body absorbs. The most commonly performed procedure at this time, which has both a restrictive and malabsorptive component, is the Roux-en-Y Gastric Bypass (RYGB). RYGB connects the upper stomach to the lower part of the small intestine, so that food bypasses a large portion of the gastrointestinal tract in which digestion and nutrient absorption normally take place. Increasingly, surgeons are performing a sleeve gastrectomy (SG) procedure in which a portion of the stomach is removed, leaving a sleeve or tube through which food can pass. Over the past several decades, researchers have sought to understand the benefits and risks of different bariatric surgery procedures.

## **The “Swedish Obese Subjects” Study of Bariatric Surgery**

One early large-scale trial was the Swedish Obese Subjects (SOS) study, which remains the largest prospective study on bariatric surgery to date. The landmark SOS study was initiated in 1987. It included more than 2,000 participants who were undergoing bariatric surgery as part of their clinical care, and, as a control group, over 2,000 individuals who had similar health-related measures at the beginning of the study but had declined surgery and instead were receiving

usual care. The researchers studied the participants over many years to compare the two groups for overall mortality, weight loss, and other important health outcomes, such as heart attacks, stroke, and type 2 diabetes. When the patients were recruited into the study (from 1987 to 2001), the most common procedure performed was vertical banded gastroplasty, a procedure which is infrequently performed today. RYGB, the most common procedure performed today, was only done in 13 percent of the SOS patients.

The SOS study now has 15 to 20 years of follow-up results. Bariatric surgery was associated with a 29 percent reduction in mortality, which was not correlated with the extent of weight loss. Type 2 diabetes remission after 2 years was 72 percent, and 36 percent after 10 years. Bariatric surgery was also associated with fewer cardiovascular events after more than 10 years. The SOS study found a reduced cancer incidence in women, but not in men, following bariatric surgery. Bariatric surgery lowered medication costs from years 7 to 20, but hospital days and outpatient visits were greater in the surgery group in the first 6 postoperative years. Although the SOS study has yielded important information about the long-term outcomes of bariatric surgery, most patients in the study underwent procedures that are no longer performed today.

## **The Longitudinal Assessment of Bariatric Surgery (LABS) Study**

Many other bariatric surgery studies have been performed over the past few decades. However, the generalizability of some of these studies has been limited by a variety of factors, such as relatively small numbers of participants, lack of diversity in geographic locations or populations, non-standardized research practices, and short-term follow-up.

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Thus, in 2003, the NIDDK began a new research effort in bariatric surgery. The Institute partnered with researchers at multiple sites across the country to create the Longitudinal Assessment of Bariatric Surgery (LABS) consortium. The goal was to facilitate and accelerate clinical, epidemiological, and behavioral research to address key long-term outcomes of bariatric surgery, with a planned follow-up of at least 5 years. Between 2004 and 2009, the multi-center LABS consortium enrolled thousands of patients with severe obesity who were already planning to undergo bariatric surgery. The geographically diverse participants were evaluated at baseline and annually with standardized measures by trained personnel to address important questions about the comparative efficacy and safety of surgical procedures, as well as the durability of weight loss and health improvements. The overall goal of this observational research was to provide evidence that can be broadly applicable to clinical practice.

LABS has already provided critical insights into the risks and outcomes of bariatric surgical procedures. One early report followed 4,776 patients with severe obesity who had bariatric surgery, from before their surgery through the first 30 days following surgery, to evaluate death and complication rates. The study took place over 2 years at 10 U.S. medical centers, with one center coordinating data collection and analysis. Within 30 days of surgery, 4 percent of patients had at least one major adverse outcome, defined as development of blood clots in the deep veins of the legs or the pulmonary artery of the lungs, repeat surgeries, not being discharged from the hospital within 30 days, or death. Mortality rates were low: fewer than 1 percent of patients died within 30 days. This evaluation highlights the level of short-term risks associated with bariatric surgery.

An important goal of the LABS consortium is to determine longer-term outcomes of bariatric surgery.

One study, reported in 2013, found that adults with severe obesity had substantial weight loss 3 years after bariatric surgery (RYGB or LAGB) with significant improvements in diabetes, high blood pressure, and cholesterol outcomes, although results varied among the study participants. A majority of the study participants lost the most weight during the first year. Overall, the median weight loss after 3 years for individuals who underwent RYGB was 31.5 percent of the body weight they had before surgery, compared with 15.9 percent weight loss for those who had LAGB surgery. Many participants had at least partial remission of type 2 diabetes, improvements in high blood pressure, and a reduction in excess fats in the blood. Although both procedures were effective, RYGB consistently led to greater health improvements than LAGB. For both procedures, fewer than 1 percent of study participants died within 3 years. Only 0.3 percent of patients who had RYGB required subsequent bariatric surgery, whereas 17.5 percent of individuals who received LAGB needed additional surgery, such as band replacement, band removal, or revision to another bariatric surgical procedure. Thus, RYGB, and to a lesser degree LAGB, leads to significant weight loss and reduction in obesity-related health conditions after 3 years, but the extent of these improvements is variable.

LABS investigators are also seeking to understand behavioral predictors and outcomes of bariatric surgery. For example, researchers found that adults who had RYGB were at significantly higher risk for alcohol use disorders (AUD) 2 years after surgery compared with before surgery. Among participants who had the RYGB procedure, there was no significant increase in AUD 1 year after surgery. By the second postoperative year, however, there was a relative increase in AUD of more than 50 percent in participants who had RYGB compared to pre-surgical rates. Patients who underwent gastric banding did



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not report an increase in AUD symptoms. While a number of predictors for AUD were identified, these results suggest that clinicians should be aware of the importance of monitoring for signs and symptoms of AUD and consider counseling after bariatric surgery, particularly in patients who undergo RYGB.

In addition to funding research on outcomes in adults, the NIDDK also supports the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. Although not common in adolescents, the use of bariatric surgery in this age group has been increasing in clinical practice. Thus, the Teen-LABS study was launched in 2007 to assess the short- and long-term risks and benefits of bariatric surgery among teens with severe obesity. This observational study enrolled 242 teens who were already planning to have bariatric surgery. The participants underwent either RYGB, SG, or gastric banding, and they were evaluated for major, life-threatening complications (e.g., bowel obstruction/bleeding, gastrointestinal leaking, deep vein thrombosis, and splenectomy), as well as for minor, non-life-threatening, complications (e.g., pneumonia, urinary tract infections or other complications, bowel injury, and hypertension). At 30 days after surgery, there were no deaths; 8 percent of the participants experienced major complications; and 15 percent experienced minor complications. Thus, over the short-term, bariatric surgery led to relatively few complications. Teen-LABS investigators will continue to study the participants to determine longer-term safety, health, and weight outcomes of bariatric surgery in teens.

## **Mining Health Databases to Evaluate Outcomes of Bariatric Surgery**

In another type of effort to gain insights on bariatric surgery outcomes from relatively large numbers of patients, researchers have sought to use data from pre-existing databases to perform retrospective

analyses. For example, one group of scientists, supported by the Agency for Healthcare Research and Quality, examined data from the electronic medical records of 1,395 adults with severe obesity and with type 2 diabetes, from 20 centers across the United States, who had bariatric surgery—most had RYGB, but a small percentage had other procedures—and more than 62,000 who did not. The goal of this study was, at 2 years after surgery, to compare various health outcomes, including diabetes remission and death. The researchers' analyses, published in 2012, showed that in this large, multi-center study, the patients who had bariatric surgery achieved higher rates of diabetes remission, with no increased risk of death, compared with patients who received usual care.

Scientists in another study, supported by the NIDDK, also used electronic medical records of 690 patients who had RYGB surgery to develop an algorithm, called the DiaRem score, that can predict the likelihood of postoperative type 2 diabetes remission. Sixty-three percent of the patients achieved partial or complete diabetes remission after the surgery. The researchers examined 259 different pre-operative clinical variables, and found that four standard measures could effectively predict type 2 diabetes remission: insulin use, age, circulating glucose levels, and type of anti-diabetes drugs. This predictive model could provide a tool for clinicians and patients to help consider whether bariatric surgery might be an appropriate treatment option, and to better manage type 2 diabetes after the operation.

## **Clinical Trials of Bariatric Surgery for Obesity and Type 2 Diabetes**

While observational and retrospective studies can provide insights about risks and benefits of bariatric surgery, proving its health impact would require long-term randomized, controlled trials (RCTs), which are

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difficult and costly to undertake. In the past few years, several relatively small RCTs enrolled participants with type 2 diabetes who either underwent bariatric surgery or were given one of a variety of non-surgical treatments for obesity and/or diabetes. After short-term follow-up, bariatric surgery procedures resulted in greater weight loss and greater remission of type 2 diabetes compared with the non-surgical options.

In addition to research focusing on people with severe obesity, recent clinical trials have been conducted to gain preliminary insights into the risks and benefits of bariatric surgery for type 2 diabetes in people with milder levels of obesity, as defined by body mass index (or “BMI,” a measure of weight relative to height). For example, reports of two small, NIDDK-supported short-term trials published in 2014 found that bariatric surgery may be more effective than non-surgical approaches for treating type 2 diabetes in adults who have moderate (BMI 35 to 40) or mild (BMI 30 to 35) levels of obesity. In one trial, 69 volunteers with type 2 diabetes were randomly assigned to receive either bariatric surgery or an intensive lifestyle intervention for weight loss, and health outcomes were compared after 1 year. About one-half of the individuals who underwent RYGB and 27 percent of those who underwent LAGB had partial diabetes remission. Their blood glucose levels were no longer in the diabetes range, and they were able to discontinue their diabetes medications. None of the people in the lifestyle intervention group had partial or complete diabetes remission. However, several individuals in the RYGB and LAGB groups experienced complications, including a surgery-related ulcer and dehydration. In another trial, investigators assigned 43 volunteers to receive either RYGB surgery or a lifestyle and medical intervention of diet and exercise, delivered in group sessions, with a weekly medication adjustment plan. After 1 year, 58 percent of the individuals in the RYGB

group, but only 16 percent of those in the lifestyle and medical therapy group, saw their blood glucose levels improve to the target for glucose control chosen as the study outcome. Weight loss was greater in the RYGB group as well. Importantly, while assessing the safety of the interventions, the researchers noted several adverse events among participants in the RYGB surgery group, including ischemic heart disease requiring coronary artery bypass surgery and depression with attempted suicide. In the non-surgical group, a few individuals experienced near-fainting.

The results of these studies were similar to other RCTs, which found improved weight and diabetes outcomes for the bariatric surgical groups when compared to those receiving non-surgical treatments for obesity or diabetes. However, RCTs are difficult to perform, generally small, and of short duration. Given these challenges, high-quality, carefully designed observational studies might be preferable to answer questions about the safety of bariatric surgery, as well as the durability of weight loss and health improvements.

## Looking Forward

While a picture may be emerging regarding the safety and efficacy of bariatric surgery as a treatment for obesity in the short- and medium-term, further research is needed to better understand the long-term risks and durability of positive outcomes. Additional avenues of clinical research, such as efforts to elucidate the behavioral and psychological factors that influence the trajectory of weight loss after bariatric surgery, could also inform clinical decisions for the treatment of obesity and its complications.

Researchers are also investigating the molecular mechanisms behind physiological changes that occur following bariatric surgery. Emerging evidence

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suggests that the beneficial effects of bariatric surgery may extend beyond the physical restrictions of the surgery, malabsorption, and the postoperative reduction of calorie intake. For example, scientists have observed near immediate improvements in type 2 diabetes and other metabolic complications prior to weight loss following bariatric surgery, but the reasons for the dramatic change in glycemic control are not yet well understood. Other physiological effects, such as alterations in the types of bacteria

that normally reside in the gut (the gut microbiome) and changes in hormones, metabolic factors such as bile acids, and nervous system pathways controlling feeding behavior and metabolism are also under investigation. These and other studies may ultimately provide the foundation for non-surgical therapies, including medications and devices, to achieve health improvements similar to those following bariatric surgery, but perhaps without the associated risks.

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## Brown and Beige Fat: Basic Biology and a Potential New Generation of Therapeutics

*Dr. Bruce M. Spiegelman*

*Dr. Bruce M. Spiegelman is the Stanley J. Korsmeyer Professor of Cell Biology and Medicine at Harvard Medical School and Dana-Farber Cancer Institute. Dr. Spiegelman received a B.S. with highest honors from the College of William and Mary, his Ph.D. in Biochemistry from Princeton University, and completed postdoctoral work at the Massachusetts Institute of Technology. Dr. Spiegelman has been honored with many awards, including the Bristol-Myers Squibb Award for Distinguished Achievement in Metabolic Research; the Solomon Berson Award, American Physiological Society; the Rolf Luft Award in Endocrinology, Karolinska Institute (Sweden); The Elliot P. Joslin Medal; the Trans-Atlantic Medal, British Endocrine Society; and the Naomi Berrie Award for Outstanding Achievement in Diabetes Research, Columbia University. He won the Banting Medal for Scientific Achievement in 2012, the highest award of the American Diabetes Association. In 2002, Dr. Spiegelman was elected to the American Academy of Arts and Sciences and the National Academy of Sciences. He was elected to the Institute of Medicine of the National Academies in 2014.*

*Dr. Spiegelman's research focuses on fat cell biology, diabetes, and the regulation of energy homeostasis in mammals, primarily at the level of gene transcription. At the February 2014 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Spiegelman presented findings from his laboratory's research; the following are highlights from his presentation.*

### **Distinct Mammalian Fat Tissues with Distinct Forms and Functions**

Mammals harbor different kinds of adipose (fat) tissue in various regions of the body. Calorie-storing white adipose tissue (WAT) is the most abundant, and can be found surrounding internal organs and under the skin. In contrast to the fat-storing WAT, brown adipose tissue (BAT) burns calories to generate heat. The heat-generating activity of brown fat is induced by cold exposure, and contributes to a phenomenon known as “non-shivering thermogenesis,” in which heat is produced as a by-product of specific biochemical processes that aid mammals in staying warm. Although human brown fat was initially thought to be present only in newborns, a series of studies have now confirmed its presence and function in adults. Recent research in rodents has identified a third type of fat cell, called beige fat (alternately called brite, for brown in white, or recruitable BAT cell), that is inducible and exhibits some of the characteristics of classic brown fat. Beige fat cells appear within portions of white fat in response to cold or other nervous system triggers.

Because brown and beige fat are capable of burning calories, Dr. Spiegelman has sought to understand whether these tissues could serve as suitable targets for the development of treatment strategies for obesity and metabolic disease. In his presentation, Dr. Spiegelman focused on two different molecules important for beige fat physiology and development that shed important new light into the molecular

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characteristics of beige and brown fat cells—the only types of cells in adult mammalian animal models known to fight diabetes and obesity by directly increasing energy expenditure.

## **The Role of PRDM16 in Beige Fat Development and Activity**

Several years ago, Dr. Spiegelman and colleagues identified a protein, called PRDM16, that is found in relatively high quantities within mouse brown fat cells, but at much lower levels in WAT. The team also showed that isolated mouse cells that ordinarily develop into brown fat cells, when depleted of PRDM16, did not develop into fat cells, as predicted, but rather became muscle cells. In the reverse experiment, mouse muscle cells converted to brown fat cells when forced (by molecular manipulation) to produce PRDM16. These studies also showed that brown fat and muscle cells have similar developmental origins, and that PRDM16 was critical for brown fat development and activity. Interestingly, Dr. Spiegelman's team characterized cells in adult human brown fat deposits, and found that these cells more closely resembled mouse beige fat than they did classical brown fat cells, highlighting the importance of understanding beige fat biology.

In mice, scientists had observed for many years brown-fat like cells embedded in WAT, but little had been known about their properties, development, and activity, primarily due to technical limitations. To better understand the role of PRDM16 in the development and activity of these cells, Dr. Spiegelman and his colleagues developed new methods to isolate and characterize beige fat cells. These techniques allowed the team to carefully define the program of genes that is turned on specifically in mouse beige fat cells. Dr. Spiegelman's group then genetically modified mice

to lack PRDM16 in brown and white fat cells (while maintaining normal PRDM16 levels elsewhere in the body), and found that the resulting mice lost the ability to induce beige fat cells in subcutaneous WAT, which is found just under the skin. Importantly, in contrast to the effects seen in beige fat tissue, the BAT did not appear to be affected by loss of PRDM16 in this model, indicating that any physiological effects were due specifically to loss of beige fat.

Further examination of the subcutaneous WAT of mutant mice under these conditions revealed that the loss of induction of beige fat cells was accompanied by a reduction in overall energy expenditure. Mutant mice that were fed a high-fat diet gained more weight over time than did normal mice. Some regions of subcutaneous fat in these mutant mice were up to twice as large as those in their normal counterparts, but the mass of visceral WAT, which surrounds internal organs, was not altered. Mutant mice also developed insulin resistance and elevated fat accumulation in the liver. Together, these findings demonstrated that, in mice, PRDM16 in WAT is required for the induction of beige fat cells, and these cells are important for metabolic health; a loss of PRDM16 impairs the “browning” of subcutaneous WAT, leading to obesity, insulin resistance, and other harmful metabolic effects when mice are fed a high-fat diet. Researchers are currently working to develop the appropriate tools and techniques to determine if humans also possess beige fat cells, and if so, how to induce their presence for potential metabolic benefit.

## **Meteorin-like: Linking Exercise to Metabolism**

Based on these and other studies, Dr. Spiegelman reasoned that activation of beige fat could improve metabolic health in human beings. However, relatively little had been known about the molecular triggers



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that induce the production and activity of these calorie-burning cells. Therefore, Dr. Spiegelman and his team sought to identify molecular signals that could promote the induction of beige fat.

The protein PGC-1 $\alpha$  is known to be critical in muscle tissue for mediating some of the molecular effects of exercise (e.g., increased mitochondrial production, breakdown of fatty acids, promotion of blood vessel development). Dr. Spiegelman's group found that one specific version of this protein, called PGC-1 $\alpha$ 4, when experimentally turned on at high levels in muscle tissue, can cause mice to become lean and more muscular. Surprisingly, PGC-1 $\alpha$ 4 elevations in muscle also turned on beige genes in WAT, suggesting that there was some communication between muscle and fat tissues that resulted in this "browning" phenomenon. Molecular tools were developed and used to search for the signal that was being sent from the muscle cells containing high levels of PGC-1 $\alpha$ 4, and the researchers identified the little-known protein hormone Meteorin-like (or "Metnl") as an important mediator of this communication. Interestingly, Dr. Spiegelman's team also found that, in both mice and humans, exercise leads to the production of Metnl in the muscle and its release into the bloodstream.

To better understand Metnl's function, the researchers generated experimentally modified mice that, in the absence of exercise, could produce the hormone—not in their muscles, but in their livers—and secrete the protein into the bloodstream. In these mice, they observed characteristic "browning" of WAT, similar to that seen in mice with high levels of PGC-1 $\alpha$ 4. The mice with liver-produced Metnl also were protected from some of the negative effects of a high-fat diet: they exhibited improved glucose (sugar) tolerance and increased energy expenditure (a physiological

feature that is associated with thermogenesis). These results showed that, in mice, Metnl signals WAT to produce physiologically active beige fat cells. An important focus of Dr. Spiegelman's ongoing research is the development of a therapeutic form of the Metnl hormone that, in humans, could help in weight loss or maintenance and improve metabolic health by triggering the "browning" of WAT.

## Conclusions

Dr. Spiegelman's research has revealed mechanisms by which beige fat is induced in WAT, leading to the "browning" phenomenon that helps protect mice from obesity and type 2 diabetes. In his talk, he described how exercise can lead to the production in muscle tissue and secretion into the bloodstream of the protein Metnl, a hormone that acts upon WAT to induce beige fat production. Dr. Spiegelman's group previously showed that a completely different hormone, called irisin, is similarly produced by muscle in response to exercise and can also promote the "browning" of WAT. However, the cellular processes by which these two hormones exert their effects on WAT are quite different, suggesting that multiple pathways work to trigger beige fat development. Once these signals from muscle tissue are received by WAT, proteins like PRDM16 are required in mice for the "browning" phenomenon; loss of PRDM16 hinders the production of beige fat cells, thereby preventing their ability to help protect the animal from metabolic disease.

Dr. Spiegelman's discoveries have illuminated multiple molecular pathways involved in brown and beige fat production. If similar pathways are employed in humans, they could be exploited for the development of potential new therapeutics to combat obesity, type 2 diabetes, and other metabolic diseases.

